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### Principles of control of cancer pain

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## ABC of palliative care

### Principles of control of cancer pain

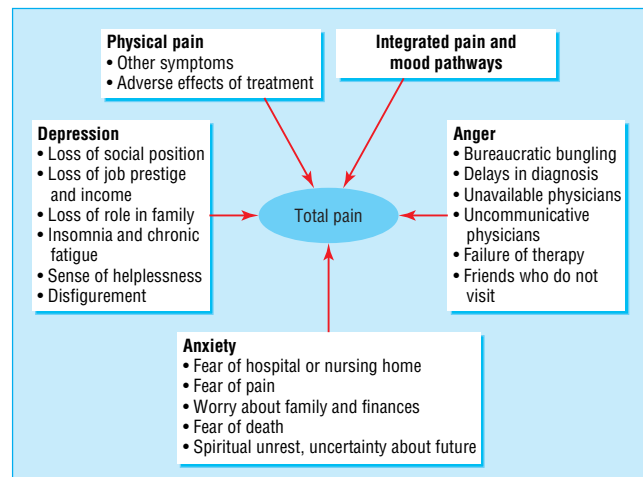
Marie Fallon, Geoffrey Hanks, Nathan Cherny

Pain is a complex phenomenon that is the subjective end point of a variety of physical and non-physical factors. For most patients, physical pain is only one of several symptoms of cancer. Relief of pain should therefore be seen as part of a comprehensive pattern of care encompassing the physical, psychological, social, and spiritual aspects of suffering. Physical aspects of pain cannot be treated in isolation from other aspects, nor can patients' anxieties be effectively addressed when patients are suffering physically. The various components must be addressed simultaneously.

Our understanding of the basic mechanisms of pain has improved considerably over the past few years. We now know that physical injury, pain pathways, and our emotional processing of this information are interlinked in the nervous system. Anxiety, fear, and sleeplessness feed into the limbic system and cortex. In turn, the brain talks back to the spinal cord modifying pain input at spinal levels. This then feeds back to the brain and a loop is established.

Mood disturbance is common in patients with uncontrolled cancer pain and may need specific management. Sometimes, however, mood will improve when the pain is resolved. Hence the first principle of managing cancer pain is a full assessment of the causes of all pain. With effective assessment and a systematic approach to the choice of analgesics using the World Health Organization's three step analgesic ladder, over 80% of cancer pain can be controlled with inexpensive drugs that can be self administered by mouth.

This article is adapted from the second edition of the *ABC of Palliative Care*, which will be published by Blackwells in the autumn and available from [www.hammicksbma.com](http://www.hammicksbma.com) and all good medical bookshops



Factors affecting patient's perceptions of pain (adapted from Twycross RG, Lack SA, *Therapeutics in terminal disease*, London: Pitman, 1984)

## WHO analgesic ladder

The analgesic ladder remains the mainstay of our approach to analgesia, although it was not designed for use in isolation. Surgery, radiotherapy, and appropriate tumoricidal treatments have an important role in some patients, as will non-drug treatments. A combined approach can lead to optimum analgesia with minimum side effects.

Analgesic drugs, however, remain key in managing cancer pain. The choice of drug should be based on the severity of the pain, not the stage of disease. Drugs should be given in standard doses at regular intervals in a stepwise fashion. If a non-opioid or, in turn, an opioid for moderate pain is not sufficient, an opioid for severe pain should be used.

When a non-opioid drug is used with an opioid for moderate pain, many patients find combination formulations more convenient. Care must be taken with the dose of each drug in the formulation; some combinations of codeine or dihydrocodeine with aspirin or paracetamol (including co-codamol and co-dydramol) contain subtherapeutic doses of the opioid. The decision to use an opioid for severe pain should be based on severity of pain and not on prognosis.

## Adjuvant analgesics

Adjuvant analgesic drugs may be usefully added at any stage. An adjuvant analgesic is a drug whose primary indication is for something other than pain but that has an analgesic effect in some painful conditions.

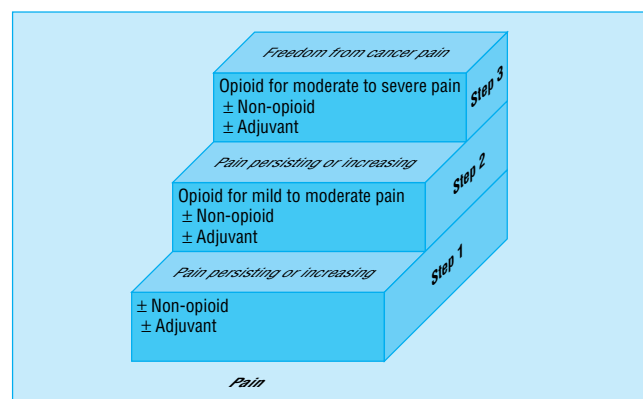
### Non-drug treatments for cancer pain

TENS (transcutaneous electrical nerve stimulation)

Physiotherapy

Acupuncture

Relaxation therapy



WHO analgesic ladder (adapted from WHO's *Cancer pain relief and palliative care*. Technical report series 804)

### Tricyclic antidepressants and anticonvulsants

Tricyclic antidepressants are sometimes helpful in relieving neuropathic pain. Efficacy is similar for all the tricyclic antidepressants, although side effects often limit their use. The evidence for venlafaxine is less strong, but it can be useful, particularly in patients with both neuropathic pain and low mood. High level evidence is lacking for use of selective serotonin reuptake inhibitors in neuropathic pain.

The anticonvulsants carbamazepine, phenytoin, sodium valproate, clonazepam, gabapentin, and pregabalin are sometimes partially effective in treating neuropathic pain. Benefit is independent of the characteristics of the pain. Gabapentin and pregabalin are licensed for neuropathic pain.

There is no measurable difference in the analgesic benefit of tricyclic antidepressants and anticonvulsants in neuropathic pain or in the number of patients needed to treat before a minor or major adverse effect occurs. Gabapentin seems to cause fewer side effects in many patients, although this has not been systematically examined in patients with cancer pain. Antidepressants and anticonvulsants may occasionally be prescribed simultaneously, although it is good practice to introduce one drug at a time.

## Opioid analgesics for severe pain

Morphine is the most commonly used opioid for severe pain. When possible, it should be given by mouth, with the tailored dose repeated at regular intervals so that the pain does not return. There is no arbitrary upper limit.

**Dose titration**—A normal release formulation of morphine (either elixir or tablet), with a rapid onset and short duration of action, is preferred for dose titration. The simplest method is to prescribe a regular four hourly dose but allow extra doses of the same size for “breakthrough pain” as often as necessary. After 24 or 48 hours, the daily requirements can be reassessed and the regular dose adjusted as necessary. This process is continued until pain relief is satisfactory. This method can take into account the many factors that contribute to the variability in dose, including severity of pain, type of pain, the affective component of pain, and variation in pharmacokinetic properties. The regular four hourly dose may range from 5–10 mg to  $\geq 250$  mg (or the equivalent in controlled release tablets). Most patients require  $< 200$  mg a day.

**Maintenance dose**—Patients with advancing disease and increasing pain may require continual adjustment of dose. Many patients, however, experience a period of stability during which the dose required remains unchanged or needs only small adjustments, and this may last for weeks, months, or sometimes longer. Once the dose is established, maintenance should be with a controlled release preparation. Controlled release morphine is available as a once daily or twice daily preparation, lasting 24 or 12 hours.

## Alternative routes of administration

The rectal bioavailability of morphine is similar to its oral bioavailability. The rectal route may be appropriate for patients unable to take drugs by mouth, and the same dose as that taken orally should be given every four hours.

For many patients unable to take drugs orally, however, it may be more convenient to convert to a subcutaneous infusion of opioid via an infusion device such as a portable, pocket sized, syringe driver. The relative potency of opioids is increased when they are given parenterally: the oral dose of morphine should be halved to get the equianalgesic dose of subcutaneous morphine and the oral dose of morphine halved or divided by

### Common adjuvant analgesics for cancer pain

Drugs	Indications
Non-steroidal anti-inflammatories	Bone pain Soft tissue infiltration Hepatomegaly
Corticosteroids	Raised intracranial pressure Soft tissue infiltration Nerve compression Hepatomegaly
Antidepressants Anticonvulsants Antiarrhythmics	Nerve compression or infiltration Paraneoplastic neuropathies
Bisphosphonates	Bone pain

### Criteria for choosing drugs for neuropathic pain

- Relative contraindications
- Possible drug interactions
- Risks of side effects

**The skilled use of morphine will confer benefit rather than harm, but many patients express fears, which should be discussed**

### Opioid alternatives to morphine

- **Hydromorphone**—Titration is usually with hydromorphone normal release capsules; when pain is controlled, patients may convert to controlled release preparation. As it is about seven times stronger than morphine, care is needed in patients with no previous exposure to opioids
- **Oxycodone**—Can be up to 1.5 times stronger than morphine. Similar titration to morphine and hydromorphone
- **Methadone**—Specialist advice should be sought
- **Fentanyl**—Self adhesive patches provide transcutaneous delivery of strong opioid. The patch is changed once every 72 hours. It is used with normal release morphine for breakthrough pain. It is suitable only for patients whose pain is stable because of the time required to titrate the dose upwards. It takes up to 24–48 hours before peak plasma concentrations are achieved
- **Buprenorphine**—Transdermal, as above, and may have advantages in patients with renal dysfunction
- **Diamorphine**, available only in the United Kingdom and Canada, is a semisynthetic derivative and a prodrug of morphine. Use of oral diamorphine is an inefficient way of delivering morphine to the body, but, for parenteral administration, its greater solubility confers an advantage over morphine
- **Pethidine** is a short acting opioid and not appropriate for the management of chronic pain



Portable syringe driver for automatic drug infusion

three, depending on the clinical situation when switching to parenteral diamorphine. Patients rarely require intravenous administration of morphine. It can, however, be appropriate for those with an indwelling central line, particularly children.

## Which opioid for cancer pain?

Comparative trials of opioids in cancer pain are very difficult to perform and do not always answer our questions because of the complexity of the populations studied. Questions also exist about the appropriateness of randomised controlled trials in patients with advanced cancer.

No strong evidence supports the superiority of one opioid over another. However, the balance between analgesia and side effects varies among opioids because of factors such as pharmacokinetic profiles, routes of administration, and genetic variability in opioid responses.

The transdermal route, which can be used with fentanyl or buprenorphine, can be useful in patients with swallowing difficulties. Oxycodone or hydromorphone may be given if morphine causes hallucinations, excessive drowsiness, or disturbed sleep.

Any opioid can accumulate in patients with renal dysfunction. Care should always be taken in such patients, and opioid doses should generally be lower than normal, with increased intervals between doses or drugs administered as required. Opioids such as fentanyl, alfentanil, hydromorphone, and buprenorphine are usually acceptable in patients with renal dysfunction but all require careful monitoring.

## Tolerance, addiction, and physical dependence

Tolerance to opioids is rarely seen in cancer patients. Requirements for increasing doses of morphine can usually be explained by progressive disease rather than tolerance.

Psychological dependence or addiction is not a problem, except in some patients with pre-existing addiction. If alternative methods of pain control are used (such as nerve blocks) the dose of the analgesic can usually be reduced, even to nothing, without adverse psychological effects. Physical dependence can occur, and this physiological response can manifest itself as a flu-like illness in some patients if an opioid is discontinued suddenly.

### Opioid toxicity

The dose of opioid that can be tolerated varies widely both between and within individuals. Although toxicity can be frightening and life threatening, it is usually reversible if it is diagnosed early.

Opioid toxicity may present as subtle agitation, seeing shadows at the periphery of the visual field, vivid dreams, visual and auditory hallucinations, confusion, and myoclonic jerks. Agitated confusion may be misinterpreted as uncontrolled pain and further opioids given. A vicious cycle follows in which the patient is given sedation and may become dehydrated, resulting in the accumulation of opioid metabolites and further toxicity.

Management includes reducing the dose of opioid, ensuring adequate hydration, and treating the agitation with haloperidol (1.5–3 mg orally or subcutaneously, repeated hourly as needed). If toxicity is severe and opioid analgesia is still needed, switching the opioid usually leads to a faster recovery. If a different opioid is required, a lower dose than the equianalgesic dose should usually be prescribed. Before the more sophisticated use of opioids, toxicity was often mislabelled as terminal agitation.

### Rationale for alternative opioids

- Basic pharmacology of the drug and particular properties relating to renal, hepatic, and cognitive impairment
- Progress in basic science, which has illuminated the genetic differences between individuals in response to opioids

### Common adverse effects of opioids

- *Sedation*—Some sedation is common at the start of treatment, but in most patients it resolves within a few days
- *Nausea and vomiting*—Nausea is common in patients taking oral morphine, vomiting rather less so. These are initial side effects and usually resolve over a few days, but they can easily be controlled—metoclopramide (10 mg every eight hours) or haloperidol (1.5 mg at night or twice daily) is effective for most patients
- *Constipation* develops in almost all patients and should be treated prophylactically with laxatives
- *Dry mouth* is often the most troublesome adverse effect for patients. Patients should be advised on simple measures to combat this, such as frequent sips of iced drinks, saliva replacements, or saliva stimulants

### Factors that affect the ability to tolerate opioids

- The degree of responsiveness of the pain to opioid analgesia
- Previous exposure to opioids
- Rate of titration of the dose
- Concomitant medication
- Concomitant disease
- Genetic factors
- Biochemical factors such as renal function

### Further reading

- Doyle D, Hanks G, Cherny NI, Calman K. *Oxford textbook of palliative medicine*. Oxford: Oxford University Press, 2003.
- Twycross RG, Lack SA. *Therapeutics in terminal disease*. London: Pitman, 1984.
- WHO Expert Committee. Cancer pain relief and palliative care. *World Health Organ Tech Rep Ser* 1990;804:1-75.

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